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RISK FACTORS OF MULTIDRUG-RESISTANT TUBERCULOSIS: A GLOBAL SYSTEMATIC REVIEW AND META-ANALYSIS

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SUMMARY

Objectives: Since the risk of multidrug-resistant tuberculosis (MDR-TB) may depend on the setting, we aimed to determine the associations of risk factors of MDR-TB across different regions.

Methods: A systematic review and meta-analysis was performed with Pubmed and Embase databases. Information was retrieved on 37 pre-defined risk factors of MDR-TB. We estimated overall Mantel-Haenszel odds ratio as a measure of the association.

Results: Factors of previous TB disease and treatment are the most important risk factors associated with MDR-TB. There was also a trend towards increased risk of MDR-TB for patients 40 years and older, unemployed, lacking health insurance, smear positive, with non-completion and failure of TB treatment, showing adverse drug reaction, non-adherent, HIV positive, with COPD and with *M. Tuberculosis* Beijing infection. Effect modification by geographical area was identified for several risk factors such as male gender, married patients, urban domicile, homelessness and history of imprisonment.

Conclusions: Assessment of risk factors of MDR-TB should be conducted regionally to develop the most effective strategy for MDR-TB control. Across all regions, factors associated with previous TB disease and treatment are essential risk factors, indicating the appropriateness of diagnosis, treatment and monitoring are an important requirements.

Keywords: MDR-TB, Risk factors, tuberculosis control, tuberculosis epidemiology

INTRODUCTION

According to the World Health Organization (WHO), tuberculosis (TB) remains a global problem with an increasing trend of new cases of TB from 6.1 million in 2015 to 6.3 million in 2016. [1] This global health problem has further worsened in recent years due to the increase in multidrug-resistant tuberculosis (MDR-TB, *M. tuberculosis* resistant to rifampicin and isoniazid), with an estimated 490 000 new patients in 2016.[1] From a health economics perspective, MDR-TB is a heavy burden on health care systems with treatment costs 20 times higher than the corresponding cost of drug-susceptible TB (DS-TB).[2]

The occurrence of drug-resistant tuberculosis (DR-TB) is not only determined by timely and correct diagnosis, adequate use of anti-TB drugs, patient factors commonly associated with drug adherence (beliefs, barriers, behavior), but also determined by microbiological factors.[3] Since spontaneous resistance mutation occurs for isoniazid and rifampicin, a combination of several TB-drugs is mandatory to avoid development of drug resistance. Although the combination of antibiotics in TB treatment can prevent acquired drug resistance to some extent, problems of adverse drug reactions (ADRs), potentially leading to treatment failure, remain a challenge worldwide.[4]

In 2014 WHO formulated globally applicable programmatic management guidelines for drug-resistant tuberculosis.[5] However, several studies reported conflicting results for some risk factors of MDR-TB.[6–11] Thus, identification of the risk factors and possible effect modification by region are needed for developing optimal intervention strategies for MDR-TB control.

Four systematic reviews and meta-analyses on risk factors for MDR-TB were performed prior to our study.[12–15] The findings of these studies were limited for several reasons. Firstly, the focus of the studies was restricted to one region and the geographical effect of the risk factors from a global perspective could not be assessed. Secondly, the risk factors were

analysed from a specific perspective, either host- or pathogen related. To support global strategies to target MDR-TB effectively, we therefore conducted a comprehensive systematic review and meta-analysis in predictive studies to determine risk factors for MDR-TB across different regions. These studies had five different perspectives, including host characteristics, previous TB disease and treatment, comorbidities, lifestyle and environmental characteristics, as well as microbiological aspects.

MATERIAL AND METHODS

Search strategy and selection criteria

A systematic review and meta-analysis study following PRISMA guidelines[16] was performed. The study was registered in PROSPERO, number CRD42016038014. We included experimental and observational predictive study designs, without language restrictions, in which one or multiple risk factors for MDR-TB were analysed during the study, from January 1, 2010, to March 26, 2016. We excluded cross-sectional studies, case reports, case series, review articles as well as conference abstract papers.

The study domain was restricted to adult TB-patients, 18 years and older. For cohort studies we included adult DS-TB patients as the population at risk, with MDR-TB as the outcome. We compared the risk factors of adult DS-TB and MDR-TB patients in included case-control studies. DS-TB was defined as fully sensitive of all anti-tuberculosis drugs to the *Mycobacterium tuberculosis* (*M.tb*) in a TB patient, while MDR-TB was defined as resistance to the first-line TB drugs rifampicin and isoniazid, with or without resistance to other first-line TB drugs. Microbiological verification was needed to confirm resistance type of the patients in this study.

We excluded studies restricted to specific high-risk MDR-TB patient groups, such as TB patients with HIV, prior TB treatment, neoplastic disease or diabetes mellitus. We also excluded studies that only used clinical or histopathological information for defining the type of TB without microbiological confirmation. Six perspectives of risk factors, comprising a list of 37 pre-defined variables in total, were analysed. The perspectives and risk factors were developed from a conceptual framework of pathogen-host-environment interplay in the emerging infectious disease [17] as well as previously published studies[12–15] providing potential targets for controlling MDR-TB. The definition criteria for the risk factors can be found in the online data supplement **Table E1**.

The outcome measure was MDR-TB defined as a resistance to the first-line TB drugs rifampicin and isoniazid, with or without resistance to other first-line TB drugs. MDR-TB status was verified by microbiological test using either phenotyping drug susceptibility test or polymerase chain reaction (PCR) based on the identification of mutations linked to resistance of *M.tb*.

Both Pubmed and Embase databases were used to find potentially eligible articles. We developed the search term and strategy together with a medical information specialist at the Central Medical Library, University of Groningen, resulting in selecting the following root terms : "tuberculosis","multiple drug resistant tuberculosis", "risk factor", "epidemiologic factor", "risk assessment", "determinant", "social determinant of health", "predictor". We used MeSH terms for the PubMed database and Emtree for the Embase database. Duplicate studies from the two databases were removed using the RefWorks® program. The comprehensive search terms are provided in the online data supplement **Table E2**.

Data abstraction and assessment of quality

Two reviewers (ISP, LDF) independently screened abstracts, full-text articles, and performed bias assessments. Disagreements between the two independent reviewers (ISP, LDF) were discussed and resolved by a third reviewer (EH). The level of disagreement was calculated using a percentage of agreement and reliability, Cohen's Kappa.[18] Data were extracted by the first reviewer (ISP) from the included articles, evaluated by the second reviewer (LDF) and final evaluation was conducted by the third reviewer (EH). We attempted to contact study authors when more data were needed; however, if the information was not received, we assumed that data were missing. We conducted a risk of bias assessment using the Risk of Bias Assessment Tool for Non-randomized studies which is compatible with the Cochrane risk of bias tool and has an acceptable validity and reliability value.[19]

Statistical analysis

A dichotomous variable was applied for each factor that was analysed. We pooled all risk factors that had a similar definition using Mantel-Haenszel Odds Ratio (mhOR) with a 95% confidence interval (95% CI). The significance threshold was set at p-value < 0·05. If data about a risk factor were only available in one study, Odds Ratio (OR) instead of mhOR was calculated. The level of heterogeneity (I^2 and p-value) was calculated to identify variation in association measures across the studies. We defined considerable heterogeneity as $I^2 \geq 75\%$[20] and/or a p-value of heterogeneity < 0·05.[21] If the data were heterogeneous, we applied a random effects model to estimate the overall effect size. Furthermore, we performed a subgroup analysis to identify sources of heterogeneity. The geographic area of the study was used for stratification in subgroup analysis. Additionally, we performed sensitivity analysis for risk factors with heterogeneous data that excluded the high potential risk of bias studies, to identify the effect size of each risk factor. Heterogeneity level and direction of the effect size among the group were considered in defining the effect estimated in the sensitivity analysis. We used Review Manager version 5.3 to analyse the effect size of the study.

RESULTS

The search process found 644 original publications from Pubmed and 764 publications from Embase. A total of 1,056 abstracts were screened after duplications were removed, and 1,036 articles were excluded for several reasons (**Figure 1**). There were 47 discrepancies between the two independent reviewers in the title-abstract screening. The level of agreement was 96% (good), and the reliability according to Cohen's Kappa was 0·78 (good). Furthermore, the disagreement arose in seven out of the 117 articles in the full-text screening, with a level of agreement of 94% (good), and reliability according to Cohen's kappa was 0·84 (good).

We found 20 studies fulfilling the inclusion criteria from the following continents; Asia (14), Africa (2), North America (1), South America (2) and Europe (1). The total number of patients included was 20 017, among which 1814 were MDR-TB patients and 18 203 DS-TB patients. Study characteristics are shown in **Table 1**.

Potential bias was analysed for the 20 included studies. Thirty percent of all included studies displayed a high potential for bias in the measurement of exposure. Interview bias, recall bias, self-reported data, and unclear definition of the exposure were identified as common sources of bias. However, the overall risk of bias was low (see supplementary **Fig. E1, E2**).

Not all pre-defined perspectives could be analysed due to lack of availability of the data in the included articles. We were not able to analyse risk factors from a health services perspective. Therefore five of the six different perspectives of risk factors, comprising 29 specific factors from the included studies, were analysed in this study. Additional data were received upon request for one study.[6] We identified significant risk factors of MDR-TB ($p<0.05$) from four perspectives, namely patient characteristics (i.e. unemployed, lacking health insurance coverage, smear positive, mantoux test positive and lung cavity), TB history

and treatment (i.e. previous TB disease, previous TB treatment, non-completion and failure of TB treatment, adverse drug reaction, non-BCG vaccination, non-adherence), comorbidity (i.e. Chronic Obstructive Pulmonary Disease, COPD) and strain (i.e. *M.tb* Beijing strain). However, several risk factors of MDR-TB showed heterogeneous results ($I^2 \geq 75\%$ or p-value heterogeneity < 0·05), i.e. age 40 years and older, male gender, married patients, lung cavity, previous TB disease, previous TB treatment, HIV, known contact with TB patients, low BMI, urban domicile, homelessness, and history of imprisonment. The pooled effect estimated for all risk factors can be found in **Table 2**.

Subgroup analysis was performed for factors with heterogeneous results to identify the effect of geographical area. When stratifying patients by setting, homogenous results appeared within subgroups for variables of gender, marital status, previous TB disease, domicile area, nature of abode, and history of imprisonment status (**Fig. 2, 3**), while heterogeneous results appeared within subgroups for variables of age, BMI, status of lung cavity, previous TB treatment, HIV and known contact with TB patients (see supplementary **Figure E3, E4**).

Subgroup analysis indicated variations dependent on setting for several risk factors of MDR-TB, such as male gender, married patients, urban domicile, homelessness, having a previous TB disease and a history of imprisonment. For example, pooled effect estimates of studies in America (Brazil and USA)[22,23] showed female patients and unmarried patients were more likely to be diagnosed with MDR-TB than DS-TB. On the contrary, effect estimates from studies in Western Asia (Iran and Israel)[7,24,25] revealed that males were more prone to MDR-TB and marital status was not a risk factor for MDR-TB in Asia (**Fig. 2A, 2B)**.[26,27] Likewise, studies from North America[23] described a protective effect of MDR-TB for subjects who had a history of imprisonment, whereas several Asian studies failed to prove any association with history of imprisonment and MDR-TB (**Fig. 3C**).[10,25,27]

Regarding variables of previous TB disease status and domicile area, we analysed that having a previous TB disease remained a significant risk factor of MDR-TB in the pooled estimate (p< 0·001; OR 4·42; 95%CI 1·46-13·37). Although risk factors of previous TB disease showed heterogeneous result (I^2: 86%), the forest plot described the same directions for a risk factor of MDR-TB in the all subgroups of variable previous TB disease (**Fig. 2C**). On the contrary, the risk factor of urban domicile differed significantly depending on the setting, where a Malaysian study indicated a protective effect of urban dwelling (p=0·03; OR 0·39; 95%CI 0·16-0·93) whereas a study in China showed an increased risk (p= 0·001; OR 1·77; 95%CI 1·42-2·21) (**Fig. 3A**).

Since heterogeneity in several variables, such as age, BMI and status of lung cavity, previous TB treatment, HIV, known contact with TB remained high (see Supplementary **Fig. E3, E4**), we therefore conducted a sensitivity analysis of these variables by excluded studies with high risk of bias. The studies that were exluded in the sensitivity analysis, i.e. studies assessing age (three studies[9,11,28]), lung cavity (five studies[8–10,29,30]), previous TB treatment (eight studies[10,11,22,24,26–29]), HIV (six studies[9–11,23,27,30]), known contact with TB (six studies[10,11,22,24,26,27]) and BMI (one study[9]). The sensitivity analysis showed being HIV positive, previous TB treatment and age 40 years and older to be risk factors of MDR-TB (**Table 3**). However, the variables 'previous TB treatment' and 'lung cavity status' displayed a heterogenous association with the risk of MDR-TB and should therefore be interpreted carefully. Regarding previous TB treatment, despite heterogeneity all effect estimates of the studies were of the same nature as risk factors of MDR-TB, while the presence of lung cavity cannot be interpreted as a risk factor for MDR-TB since effect estimates across studies showed conflicting results (supplementary **Fig. E4B)**.

DISCUSSION

We identified an effect modification by geographic area for several risk factors of MDR-TB, such as male gender, married patient, urban domicile, homelessness and having a history of imprisonment. Our results confirm prior reviews that having a previous TB disease and treatment are the most influential risk factors for developing MDR-TB, independent of the setting. Furthermore, patients 40 years and older, lacking health insurance, unemployed, non-adherent, ADRs, with a history of non-completion or failure of TB treatment, without BCG vaccination, HIV positive, with COPD, with infection with *M. tb* Beijing strain, smear and mantoux test positivite, show significant risk factors for developing MDR-TB. On the contrary, other risk factors identified in prior studies, such as, low education status, non-Directly Observed Treatment (DOT), diabetes mellitus, cardiovascular diseases, hepatitis, known contact with TB patients, smoking, low BMI and daily alcohol intake, did not show a clear association with MDR-TB in our study.

In terms of microbiological aspect, our study was supported by other studies. Beijing *M. tb* strains are more likely to be MDR-TB than non-Beijing *M. tb* strains, according to studies from Indonesia,[31] Vietnam,[32] and Russia,[33] linking the *M. tb* Beijing genotype strain with a history of previous TB treatment and treatment failure. Animal studies have shown Beijing *M. tb* strains to be more virulent with more extensive tissue destruction, rapid outgrowth, and increased mortality.[34] Suggested hypotheses for this association regard differences in cell wall structure, leading to suboptimal intracellular drug concentrations, as well as a higher virulence *per se*, resulting in longer persistent infection.[35]

Regarding comorbidities, it is a matter of debate whether HIV is a risk factor for MDR-TB. A previous systematic review showed no association between HIV and primary or secondary MDR-TB.[36] However, our study indicated that HIV is a risk factor for MDR-TB after sensitivity analysis was performed. This can be explained by both immune status and drug-

related factors. Immunosuppression can lead to reactivation of latent TB, increased risk of re-infection recurrence due to new *M.tb* infection and rapid progression to active TB.[37] Furthermore, problems relating to drug interactions, overlapping drug toxicities, high pill burden, drug malabsorption and immune reconstitution inflammatory syndrome (IRIS) can potentially lead to the development of drug resistance and therapeutic failure in co-infected TB-HIV patients.[38] Hence, there is biological plausibility for HIV being a risk factor of MDR-TB and this finding has been supported by Faustini and co-authors, showing that HIV is associated with MDR-TB (OR 3·5; 95% CI 2·48-5·01).[14]

Another comorbidity, COPD, has also been discussed as a risk factor of MDR-TB. A prospective study of pulmonary tuberculosis (PTB) patients aged ≥ 40 years with concomitant COPD had an increased risk of developing MDR-TB. [39] There is also evidence of an inverse relationship; TB patients can develop COPD as a result of long-term damage of structural and functional of the lung.[40,41] In our study, we analysed two case-control studies from Malaysia and USA, with 120 MDR-TB patients as cases and 2,186 DS-TB patients as controls. Our study indicated that COPD patients were more likely to have MDR-TB than patients without COPD, with a pooled estimate 2.5 times higher for COPD patients than non-COPD patients.

Our study demonstrated that failed TB treatment is a considerable risk factor for MDR-TB. Although non-adherence to treatment is believed to be a cause of treatment failure in TB patients, a pre-clinical study showed that non-adherence alone was not sufficient for the development of MDR-TB, but in-between patient pharmacokinetic variability was necessary.[42] Similarly, a meta-analysis identified pharmacokinetic variability of isoniazid to be associated with therapeutic failure and acquired drug resistance.[43] Another meta-analysis analysed genetic factors such as rate of acetylation, where patients who have rapid acetylation of isoniazid were more likely to have microbial failure, acquire drug resistance and relapse than patients with slow acetylation.[43] On the other hand, patients with a slow isoniazid

acetylation profile were more prone to hepatotoxicity than patients with a rapid acetylation profile.[44] It is apparent that pharmacogenetics variation plays an important role in therapeutic response and ADRs, besides inter-individual variability of pharmacokinetics profile.[44]

Our study corroborated the results of prior meta-analyses showing that previous TB disease and treatment were essential risk factors of MDR-TB, while alcohol abuse and low education were not.[12–14]Moreover, meta-analyses in China pointed out pulmonary cavity and living in rural area as risk factors of MDR-TB,[12,13] while studies in Europe showed that male gender, homelessness and urban domicile to be risk factors of MDR-TB.[14] As described in the aforementioned studies, the impact of risk factors can differ according to geographical area.

Our study suggests that identifying risk factors of MDR-TB regionally is important in developing strategies for MDR-TB control as a result of regional differences in the risk factors due to variation of healthcare quality, socio-behavioral and poor living conditions. Since unemployment and lack of health insurance coverage are risk factors of MDR-TB in our study, government support is crucial to organise universal health coverage that will cover not only drug cost but also diagnosis, treatment and monitoring for TB patients. In addition, enhancing access to health facilities and laboratories, including qualified drug susceptible tests, are required for appropriate diagnosis and treatment as well as for correct surveillance of the MDR-TB epidemic.

The fact that we identified non-adherence, previous and failed TB treatment as considerable risk factors of MDR-TB in our study, indicates that variation of adherence, pharmacokinetics and pharmacogenetics profile among TB patients is a factor that should be considered to avoid development of MDR-TB. Antibiotic stewardship program for drug-resistant tuberculosis is required to be established at an institution level, specifically in high-burden areas of TB. The collaborative team should include physicians, pharmacists, microbiologists, nurses and administrators, all with a common goal to improve diagnosis,

treatment and monitoring of TB patients. Personalised treatment could be a promising approach for controlling MDR-TB, especially in patients at high risk of MDR-TB. Therapeutic drug monitoring and intervention with individual non-adherence can be implemented as a program to achieve treatment success.[45] However, since personalised treatment needs advanced resources, free consultation of TB experts should be widely available for health care providers to make rapid decisions on the management of complex TB cases, particularly in an area with limited resources.

There are several limitations in our study. Firstly, most of our included studies were case-control studies where recall bias may have occurred. Secondly, not all countries and included risk factors could be assessed due to unavailability of data. Thirdly, since the majority of studies were predictive studies, the causality of risk factors and outcome should be explored further using an appropriate study design. Finally, the power of the study was low for some risk factors of MDR-TB, such as non-BCG vaccination and positive Mantoux test. We noticed a potential information bias due to missing data in the only included study which analysed positive Mantoux test as a risk factor for MDR-TB. The study showed a high proportion of participants who had unknown information of Mantoux test results in the MDR-TB group (58.8%). The multivariate analysis indicated that Mantoux test positivity and non-BCG vaccine status were not significant risk factors for MDR-TB. ($p \geq 0 \cdot 05$).[10,26] Hence, there is no clear support of an association of Mantoux test and BCG vaccination with MDR-TB.

On the other hand, we performed a thorough full-text screening, excluding studies with a high level of bias in the sensitivity analysis. We also assessed statistical heterogeneity and biological plausibility from the current evidence. Furthermore, we attempted to contact study authors to obtain more comprehensive data in our study.

In conclusion, factors of previous TB disease and treatment are the major risk factors for MDR-TB across all settings. Subsequently, we identified patients age 40 years and older,

unemployed, lacking health insurance, smear positive, with a history of non-completion and failure of TB treatment, with adverse drug reaction, non-adherent, HIV positive, with COPD and with *M. Tuberculosis* Beijing infection who should be carefully monitored during their TB treatment to avoid development of MDR-TB. Equally important, risk factors of MDR-TB related to male gender, married patient, urban domicile, homelessness and having a history of imprisonment can vary depending on the setting. Therefore, assessment of risk factors of MDR-TB should be conducted regionally to develop the most effective strategy for MDR-TB control.

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Conflict of interests

ISP, LDF, JB, EH and JWA have no competing financial or non-financial interests in this work

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FIGURES AND TABLES

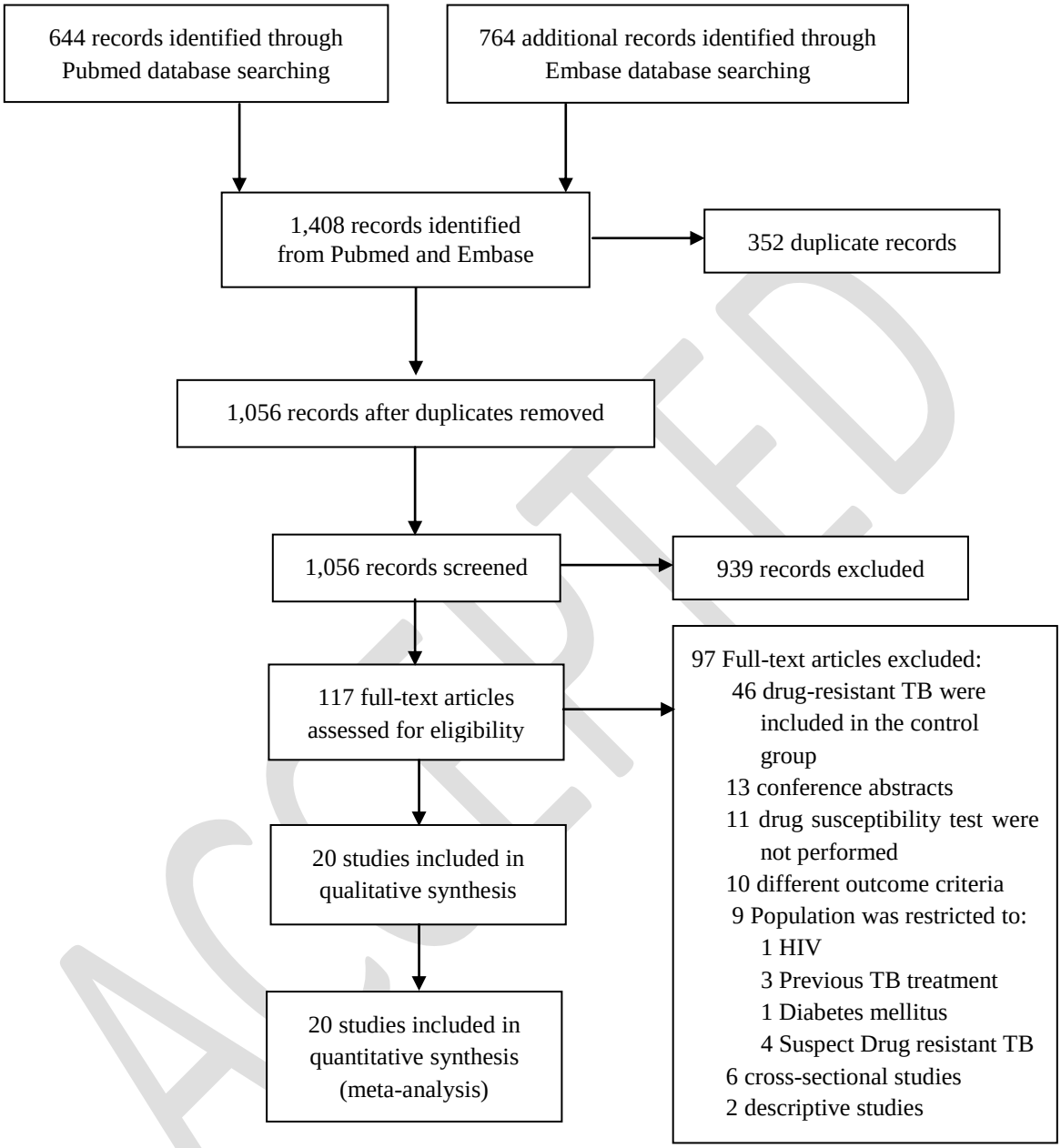
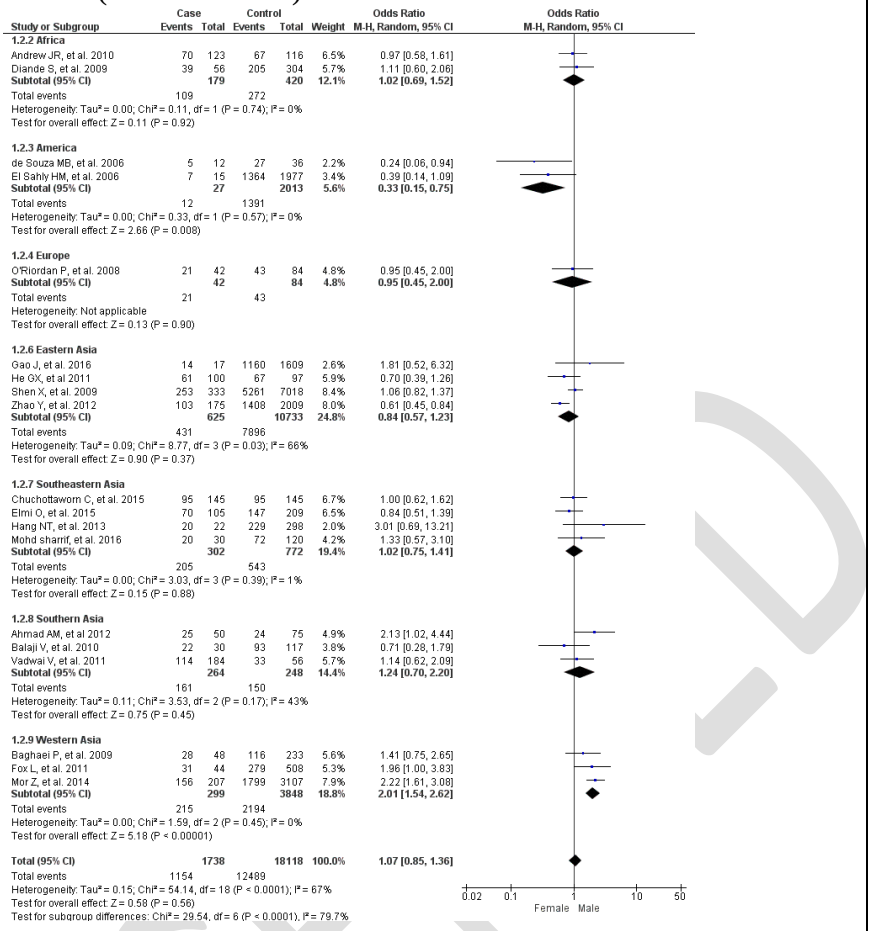
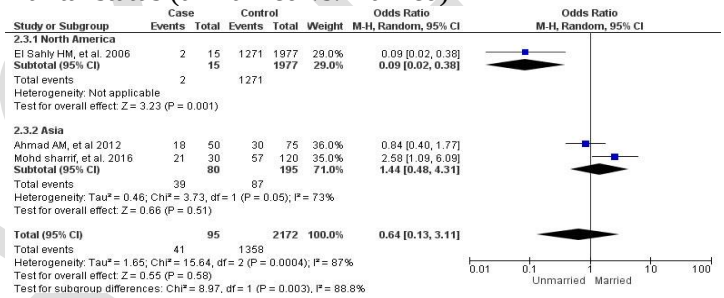


Figure 1. Flow diagram, literature search and screening process.

A. Gender (female vs. male)



B. Marital status (unmarried vs. married)



C. Previous TB disease (non-previous TB disease vs. previous TB disease)

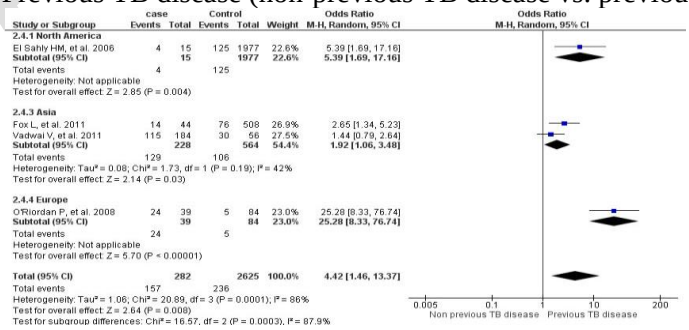
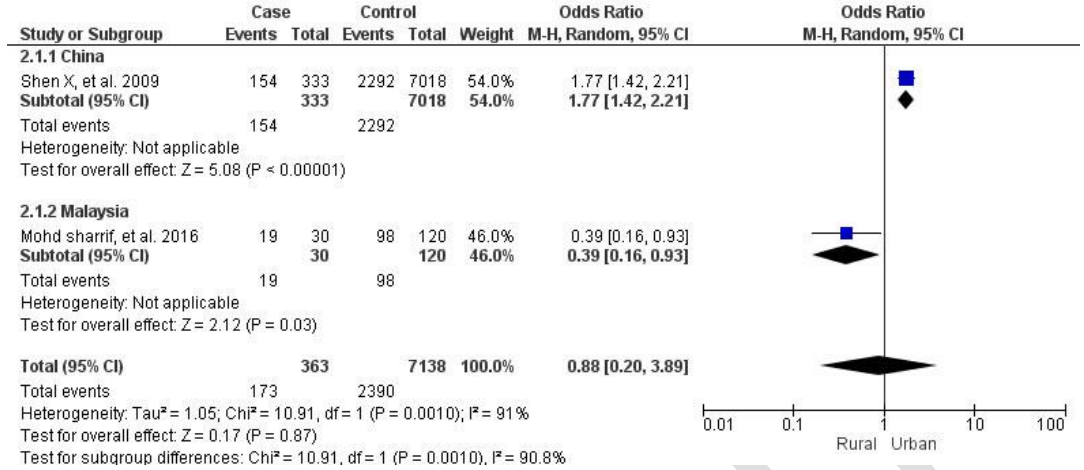
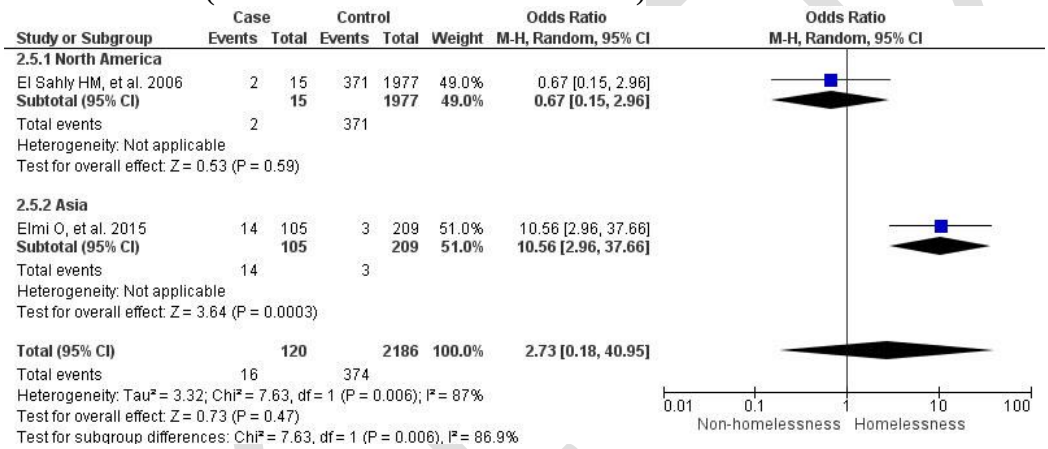


Figure 2. Homogeneous effect estimated within the subgroup of gender, marital status and previous tuberculosis disease, stratified by area of study. *Notes*: reference group in each of factors: (A) female, (B) unmarried (C) non-previous TB disease; Citation of the studies refers to Table 1.

A. Domicile area (rural vs. urban)



B. Nature of abode (non-homelessness vs. homelessness)



C. History of imprisonment (non-history of imprisonment vs. history of imprisonment)

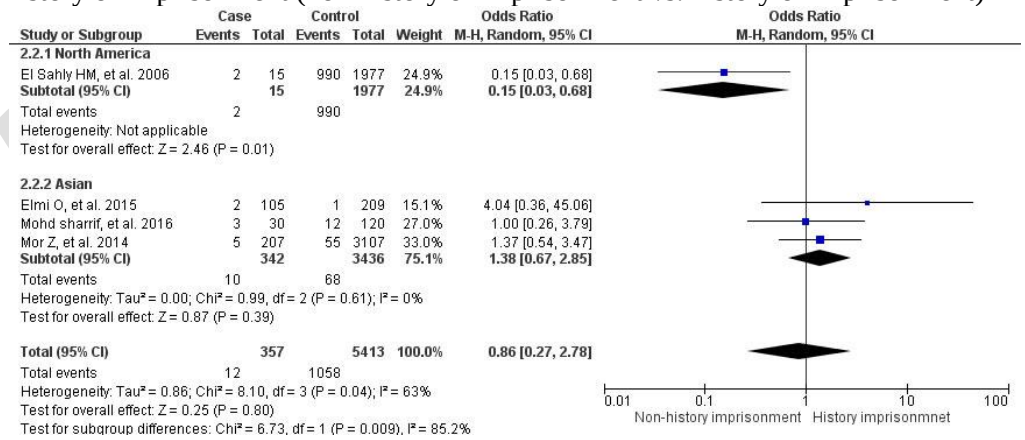


Figure 3. Homogeneous effect estimated within the subgroup of domicile area, nature of abode and history of imprisonment, stratified by area of study. *Notes*: reference group in each of factors: (A) rural domicile, (B) non-homelessness, (C) non-history of imprisonment Citation of the studies refers to Table 1.

Table 1. Characteristics of the studies included in the systematic review and meta-analysis.

Author (year publication)	Country	Study design	Study period	Case (MDR-TB)	Control (DS-TB)	Risk factors identified
Ahmad et al. (2012)[26]	Pakistan	Case-control	2000-2002	50	75	Marital status, gender, non-BCG vaccination, previous treatment, smoking, known contact with TB patient
Andrew et al. (2010)[46]	South Africa	Case-control	2005-2007	123	116	Gender, non-completion and failure of TB treatment, HIV
Baghaei et al. (2009)[24]	Iran	Case-control	2002-2005	48	234	Gender, previous treatment, smear positivity, smoking, known contact with TB patient
Balaji et al (2010)[30]	India	Case-control	2002-2007	30	117	Gender, lung cavity, HIV
Chuchottaworn et al. (2015)[9]	Thailand	Case-control	2007-2013	145	145	Age 40 years and older, gender, non-completion and failure of TB treatment, CVD, DM, HIV, low BMI
De Souza et al. (2006)[22]	Brazil	Case-control	2000-2004	12	36	Employment status, gender, previous treatment, smear positivity, DM, HIV, known contact with TB patient, daily alcohol consumption
Diande et al. (2009)[11]	Burkina Faso	Case-control	2005-2006	56	304	Age 40 years and older, employment status, gender, previous treatment, HIV, known contact with TB patient, daily alcohol consumption

El Sahly et al. (2006)[23]	The United States	Case-control	1995-2001	15	1977	Marital status, gender, previous TB disease, COPD, HIV, history of imprisonment, history homeless, daily alcohol consumption
Elmi et al. (2015)[10]	Malaysia	Case-control	2010-2014	105	209	Gender, previous treatment, COPD, Mantoux test positivity, lung cavity, HIV, history of imprisonment, smoking, history of homeless, known contact with TB patient, daily alcohol consumption
Ferro et al (2011)[47]	Colombia	Case-control	2007-2008	76	84	*M. tb* Beijing genotype strain
Fox et al. (2011)[7]	Israel	Case-control	2002-2009	44	508	Gender, DOT, non-completion and failure of TB treatment, previous TB disease, hepatitis, lung cavity, HIV
Gao et al (2016)[48]	China	Cohort	2008-2010	17	1609	Age 40 years and older, gender, ADRs, previous treatment, low BMI
Hang et al. (2013)[6]	Vietnam	Case-control	2007-2009	22	298	Gender, HIV smoking, *M. tb* Beijing genotype strain
He et al. (2011)[49]	China	Case-control	2007-2009	100	97	Non-coverage health insurance, gender, previous treatment, lung cavity, known contact with TB patient, *M. tb* Beijing genotype strain
Mohd Sharrif et al. (2016)[27]	Malaysia	Case-control	2013-2014	30	120	Marital status, gender, non-adherence, higher education, previous treatment, smear positive, DM,

						HIV, history of imprisonment, smoking, urban area, known contact with TB patient, daily alcohol consumption
Mor et al. (2014)[25]	Israel	Case-control	1999-2000	207	3107	Gender, previous treatment, smear positivity, HIV, history of imprisonment
O'Riordan et al. (2008)[50]	England	Case-control	1982-2004	42	84	Gender, previous TB disease, smear positivity, known contact with TB patient
Shen et al. (2009)[29]	China	Case-control	2000-2006	333	7018	Gender, previous treatment, smear positivity, lung cavity, urban area
Vadwai et al. (2011)[8]	India	Case-control	2009	184	56	Gender, previous TB disease, lung cavity, HIV
Zhao et al (2012)[28]	China	Case-control	2004-2005	175	2009	Age 40 years and older, gender, previous TB treatment

Notes: MDR-TB: multidrug-resistant tuberculosis; DS-TB: drug-susceptible tuberculosis; BCG: *Bacille Calmette-Guérin*; HIV: human immunodeficiency virus; CVD: cardiovascular; DM: diabetes mellitus; BMI: body mass index; COPD: chronic obstructive pulmonary disease; *M.tb*: *Mycobacterium tuberculosis*; DOT: directly observed treatment; ADRs: adverse drug reactions.

Table 2. Effect estimates for risk factors of Multidrug-Resistant Tuberculosis (MDR-TB)

Risk factors	Number of Studies	Participants	Effect Estimated Odds Ratio (95% CI)	Heterogeneity I^2 (p-value)
Patients characteristics				
Age 40 years and older	4[9,11,28,48]	4460	1·34 (0.75-2.39)	76% (0·006)[†]
Male gender	19[6–11,22–30,46,48–50]	19 856	1·07 (0·85-1.36)	67% (<0·001)[†]
Higher education	1[27]	150	1·69 (0·73-3·87)	n/a
Unemployment	2[11,22]	408	3·00 (1·69-5·30)[*†]	69% (0·07)
Lack of health insurance coverage	1[49]	197	1·99 (1·12-3·54)[†]	n/a
Married patient	3[23,26,27]	2267	0·64 (0·13-3·11)	87% (< 0·001)[†]
Smear positive	6[22,24,25,27,29,50]	11 161	1·72 (1·40-2·12)[*†]	41% (0·13)
Mantoux test positive	1[10]	103	3·38 (1·45-7·89)[†]	n/a
Lung cavity	7[7–10,29,30,49]	8825	1·92 (1·02-3·62)[†]	89% (< 0·001)[†]
TB history & treatment				
Presence of previous TB disease	4[7,8,23,50]	2907	4·42 (1·46-13·37)[†]	86% (< 0·001)[†]
Presence of previous TB treatment	11[10,11,22,24–29,48,49]	15 657	7·24 (4·06-12·89)[†]	88% (< 0·001)[†]
Non-completion and failure of TB treatment[‡]	3[7,9,46]	1354	5·60 (3·36-9·32)[*†]	0%; (0·37)
DOT program	1[7]	552	1·36 (0·47-3·95)	n/a
Presence of adverse Drug Reaction	1[48]	552	2·31 (1·14-4·69)[†]	n/a
Non-BCG vaccination	1[26]	125	2·79 (1·13-6·85)[†]	n/a
Non-adherence	1[27]	150	4·50 (1·71-11·82)[†]	n/a
Disease or comorbidity				
HIV positive	11[6–11,23,25,27,30,46]	10 736	1·49 (0·73-3·06)	81% (< 0·001)[†]

Diabetes mellitus	4[9,10,22,27]	802	1·30 (0·91-1·86)[*]	44% (0·15)
Cardiovascular disease	1[9]	290	0·75 (0·36-1·58)	n/a
COPD	2[10,23]	2306	2·53 (1·05-6·14)[*†]	40% (0·20)
Hepatitis	1[7]	552	0·42 (0·13-1·40)	n/a
Life style& Environmental				
Known contact with TB patient	8[10,11,22,24,26,27,49,50]	1453	1·30 (0·74-2·29)	67% (0·004)[†]
Smoker	5[6,10,24,26,27]	1189	0·90 (0·66-1·22)[*]	21% (0·28)
Low BMI**	2[9,48]	1865	0·86 (0·17-4·27)	82% (0·02)[†]
Urban domicile	2[27,29]	7501	0·88 (0·20-3·89)	91% (< 0·001)[†]
Daily alcohol consumption	5[10,11,22,23,27]	2720	0·80 (0·49-1·30)[*]	49% (0·10)
Homelessness	2[10,23]	2306	2·73 (0·18-40·95)	87% (0·006)[†]
History of imprisonment	4[10,23,25,27]	5770	0·86 (0·27-2·78)	63% (0·04)[†]
Strain				
Beijing strain	3[6,47,49]	665	5·58 (1·66-18·76)[*†]	66% (0·05)

Notes: * Fixed effect model; [†]Significant value ($p < 0.05$); [‡]including non-cure, non-completion, default and failure treatment; ** Body Mass Index (BMI) < 18 kg/m^2; n/a : not applicable; COPD: Chronic obstructive pulmonary disease; HIV: Human Immunodeficiency Virus; DOT: Direct Observed Treatment.

Table 3. Sensitivity analysis of heterogeneous' factors**.**

No	Risk factors	Pre-sensitivity analysis			Post-sensitivity analysis		
		Number of Studies	**Odd Ratio (95% CI)**	**I^2 (p-value)**	**Number of Studies**	**Odd Ratio (95% CI)**	**I^2 (p-value)**
1	Age 40 years and older	4	1·34 (0·75-2·39)	76% (0·006)†	1	14·18 (1·88-107·18) †	n/a
2	Lung cavity	7	1·92 (1·02-3·62)†	89% (< 0·001) †	2	1·10 (0·40-3·02)	82% (0·02) †
3	Presence of previous TB treatment	11	7·24 (4·06-12·89) †	88% (< 0·001) †	3	5·38 (1·67-13·37)†	80% (0·007)†
4	HIV positive	11	1·49 (0·73-3·06)	81% (< 0·001) †	5	3·04 (1·60-5·77) †	55% (0·08)
5	Known contact with TB patient	8	1·30 (0·74-2·29)	67% (0·004) †	2	0·80 (0·22-2·85)	58% (0·12)
6	Low BMI	2	0·86 (0·17-4·27)	82% (0·02) †	1	0·34 (0·10-1·19)	n/a

Notes : I^2: heterogeneity; †Significant value; Low body mass index (BMI) : BMI < 18 kg/m^2; 95%CI : 95% confidence interval; HIV: Human Immunodeficiency Virus; TB: tuberculosis

ONLINE DATA SUPPLEMENT

Title : Risk Factors of Multidrug-Resistant Tuberculosis: A Global Systematic Review and Meta-Analysis

Authors : Ivan S. Pradipta, Lina D. Forsman, Judith Bruchfeld, Eelko Hak, Jan-Willem Alffenaar.

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Table E1. Exposure criteria of systematic review and meta-analysis study on risk factors of multidrug-resistant tuberculosis

No	Perspectives	Exposure/Risk factor	Operational Definition
1	Patients characteristics	Age	Age of the participants, divided between < 40 and ≥ 40 years old
		Gender	Male or female
		Level of education	Categorized as lower education (below diploma level or non-education) and higher education (diploma, bachelor, master or doctoral degree)
		Knowledge of MDR-TB	Participants who can explain the basic understanding of tuberculosis and MDR-TB correctly, i.e., signs, symptoms, process of TB spreading, the definition of MDR-TB and awareness of the long treatment duration is identified as good knowledge.
		Occupation	Occupation of the participants
		Marital status	Married or unmarried
		Lack of health insurance	Participants who have no health insurance coverage
2	Tuberculosis (TB) history and treatment	Previous treatment	Participants who have received at least one month of anti-Tb drugs in the past, regardless of their treatment outcome.
		Previous TB disease	Participants with a history of previous TB, regardless of treatment status
		Non-completion and failure of TB treatment	Participants who have one of the criteria below : • non-completion: participants who discontinued/ stopped treatment before defined period of treatment, OR • non-cure or failure treatment: a patient who is sputum smear or sputum culture positive at five months or later after the initiation of anti TB treatment, OR • default: participants who have interrupted TB treatment for two or more consecutive months
		Fixed Dose Combination (FDC)	Participants treated with FDC rather than multiple single anti-tuberculosis drug use

		Route of administration	Intravenous versus oral treatment
		Adverse drug reactions (ADRs)	Participants who experienced ADRs during TB treatment
		Previous BCG vaccination	Participants who had a previous BCG-vaccination.
		Non-adherence	Participants who completed the duration of treatment, who however took less than 90% of the prescribed anti-tuberculosis drug without clinical reasons, such as adverse drug reaction or drug interaction.
3	Comorbidities	Human Immunodeficiency Virus (HIV)	Clinically or lab-confirmed diagnosis of HIV
		Diabetes mellitus (DM)	Diagnostic criteria of fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or 2-h plasma glucose ≥ 11.1 mmol/l (200 mg/dl) or diagnosed DM by the clinician.
		Chronic Obstructive Pulmonary Diseases (COPD)	Clinically confirmed diagnosis of COPD, including emphysema, chronic bronchitis, refractory (non-reversible, asthma, and bronchiectasis).
		Cardiovascular diseases (CVD)	Includes diagnoses such as previous heart attack, ischemic stroke, heart failure, arrhythmia, and health valve disease
		Hepatitis	Any viral hepatitis with laboratory confirmation or stated in medical records by a medical doctor.
		Liver diseases	Any diagnosis of liver disease and/or three times elevated the normal value of Alanine Transaminase (ALT) in the blood (ref 7-56 unit/L)
		Lung cavity	Presence of lung cavity on chest x-ray
		Hypoalbuminea	Plasma albumin < 35 g/dL
		Sputum smear positivity	Visible *M. tb* in the sputum during microscopy (Ziehl-Neehlsen or auramine stain)
		Low Body Mass Index (BMI)	BMI < 18 Kg/m^2
		Positive Mantoux test	A positive tuberculin skin test, defined according to a medical doctor's interpretation after dermal

			injection of protein derivative of tubercle bacillus, with a raised red area of 5-10 mm appearing 48-72 hours[51].
4	Lifestyle and Environmental	Smoking	Including former and current smoking habit, regardless of duration
		Known contact with TB patient	Known previous contact with a patient diagnosed with contagious TB
		Daily alcohol consumption	Participants who consume alcohol on a daily basis
		Nature of abode	It is divided into homelessness and non-homelessness. Homelessness is defined as participants who have a previous or current history of homelessness
		History of imprisonment	Participants who are currently imprisoned or have a previous history of imprisonment.
		Domicile area	Domicile area of the participant. It is divided into two categories, i.e. urban domicile and rural domicile.
		Room spaces	Total number of rooms in the household
5	Microbiology	Beijing strain	*M. tb* type Beijing strain
6	Health services	Accessibility of health facility	Distance and travel time to the health facility
		Drug supply	Availability of anti-tuberculosis drugs in the health facility
		Low-quality medicines	Low quality of medicine refers to counterfeit and/or poor quality anti-TB drugs based on physical and chemical criteria of the drug.

Table E2. Search terms of the study.

No	Bibliographic database	Key terms
1	Pubmed	((((("Tuberculosis, Multidrug-Resistant"[Mesh] OR multidrug resistant tuberculosis[tiab] OR mdr tb[tiab] OR mdr tuberculosis[tiab] OR mdr-tb[tiab] OR multi drug resistant tuberculosis[tiab] OR multi-drug resistant tuberculosis[tiab] OR multiple drug resistant tuberculosis[tiab])) AND ("Risk Factors"[Mesh] OR "Epidemiologic Factors"[Mesh] OR predictor*[tiab] OR determinant*[tiab] OR risk factor*[tiab] OR epidemiologic factor*[tiab]))) NOT ("Cross-Sectional Studies"[Mesh] OR cross-sectional [tiab] OR cross sectional [tiab] OR crosssectional [tiab]) *Filters*:Publication date from 2006/01/01 to 2016/03/26
2	Embase	# 1 'risk assessment'/exp OR 'risk assessment' OR 'risk factor'/exp OR 'risk factor' OR 'predictor variable'/exp OR 'predictor variable' OR 'social determinants of health'/exp OR 'social determinants of health' OR 'risk factor':ab,ti OR 'risk factors':ab,ti OR 'epidemiologic factor':ab,ti OR 'epidemiologic factors':ab,ti OR 'predictor*':ab,ti OR 'determinant*':ab,ti #2 'multidrug resistant tuberculosis'/exp OR 'multidrug resistant tuberculosis':ab,ti OR 'mdr tb':ab,ti OR 'multi-drug resistant tuberculosis':ab,ti OR 'mdr-tb':ab,ti OR 'mdr tuberculosis':ab,ti OR 'multi drug resistant tuberculosis':ab,ti OR 'multiple drug resistant tuberculosis':ab,ti #3 'cross-sectional study'/exp OR 'cross-sectional study' OR 'cross sectional':ab,ti OR 'çross-sectional':ab,ti OR 'crosssectional':ab,ti ((#1 AND #2) NOT #3) AND [2006-2016]/py

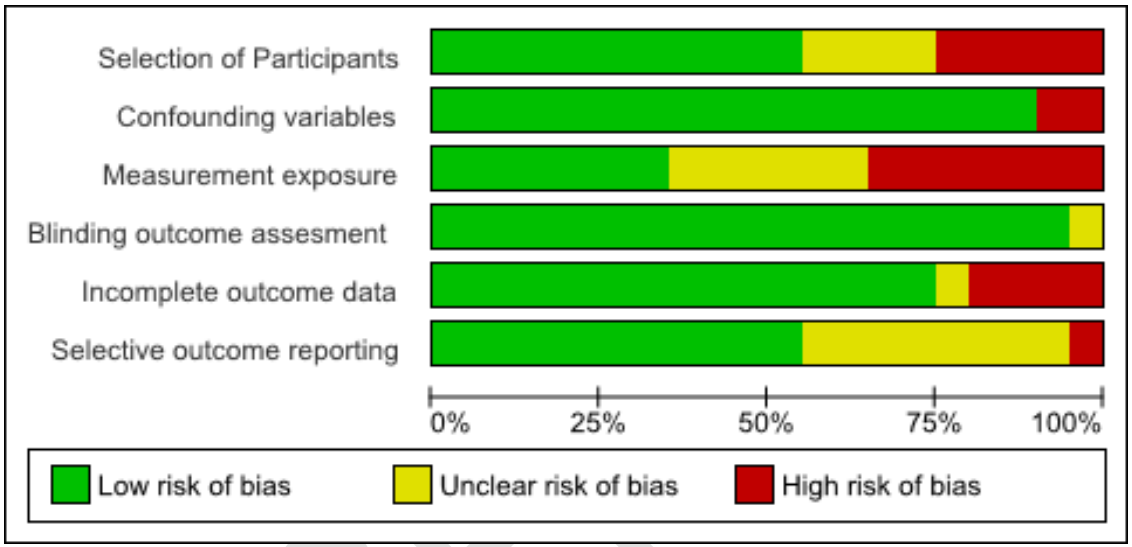


Figure E1. Risk of bias graph: review authors' judgments about the risk of bias per variable, presented as percentages across all included studies.

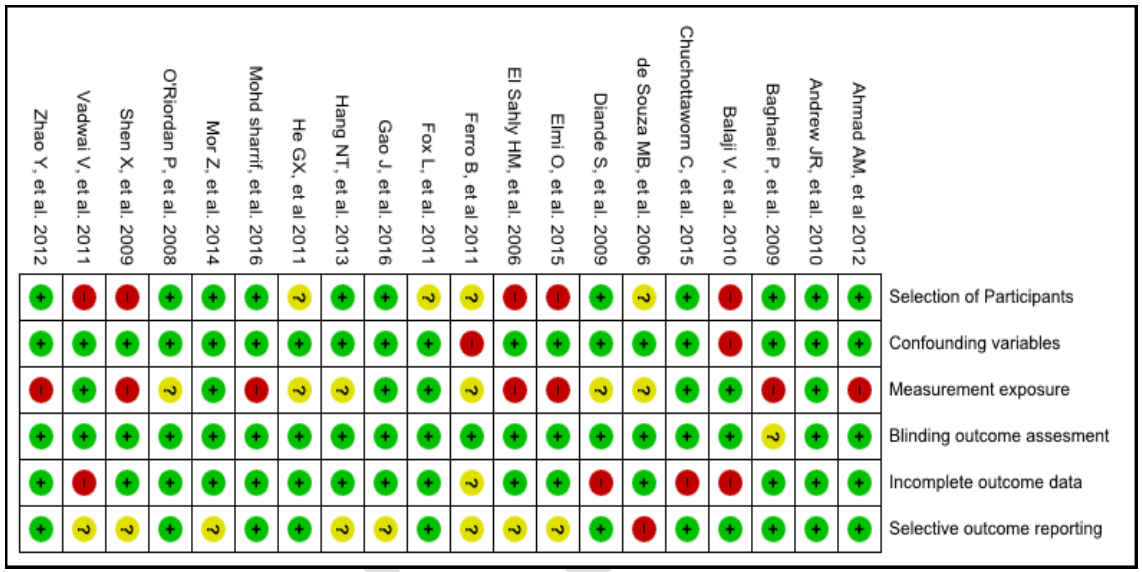
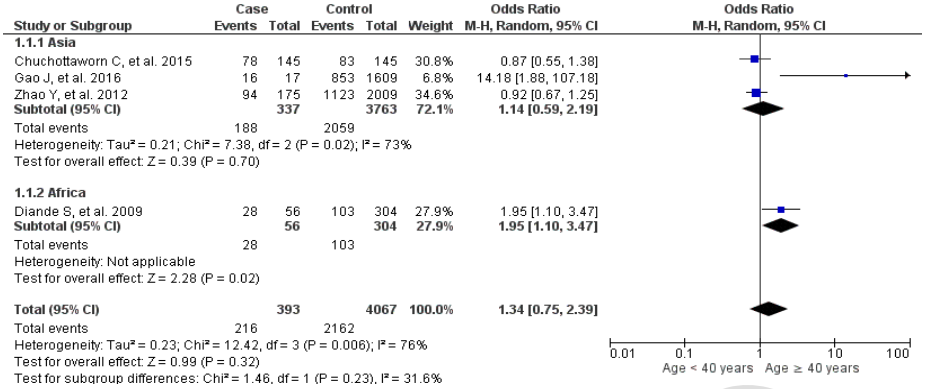
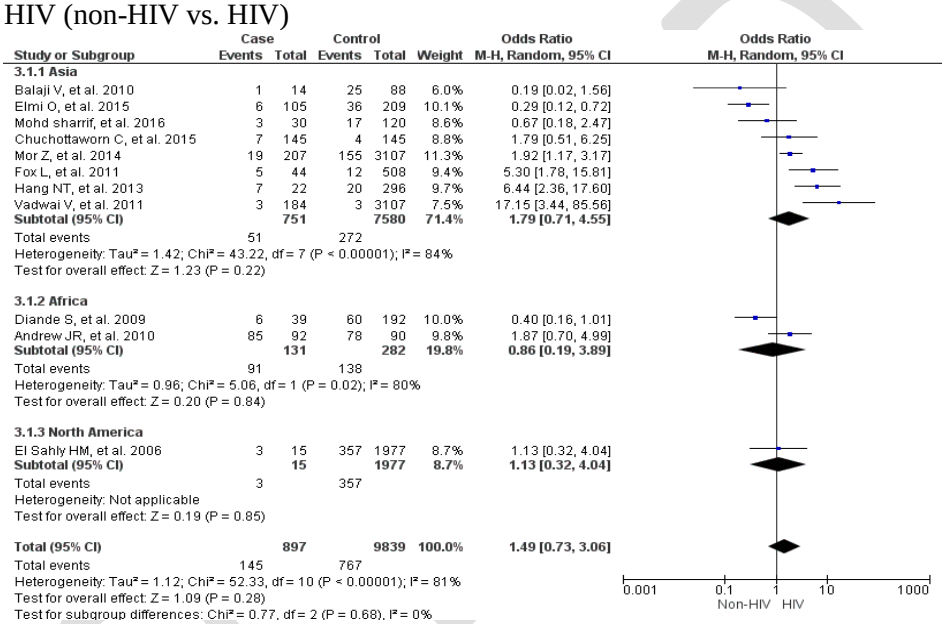


Figure E2. Risk of bias summary: review authors' judgment about each risk of bias item for each included study.
Notes: Green (+) shows low risk of bias, yellow (?) shows unclear risk of bias, and red (-) shows high potential risk of bias. *Notes*: Citation of the studies refers to Table 1.

A. Age (< 40 years vs. ≥ 40 years)



B. HIV (non-HIV vs. HIV)



C. Previous TB treatment (non-previous TB treatment vs. previous TB treatment)

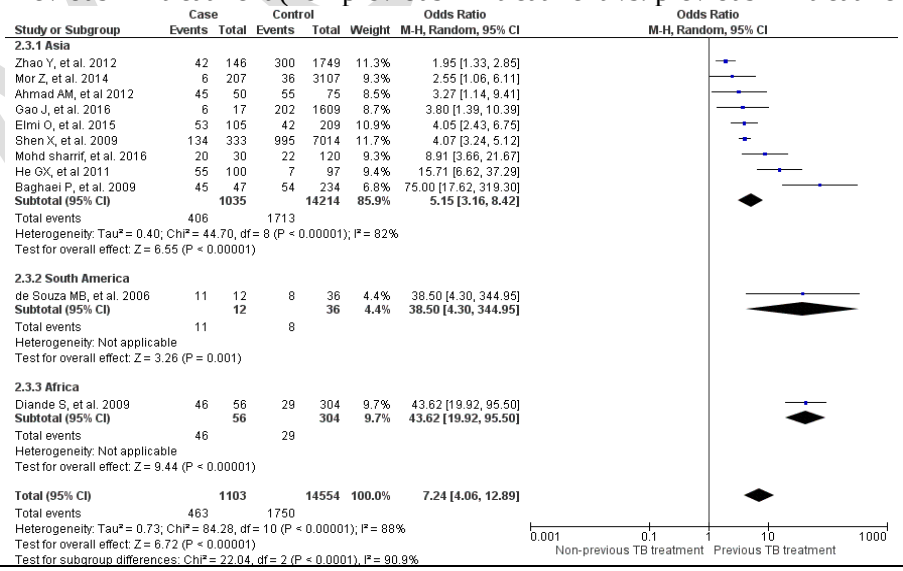
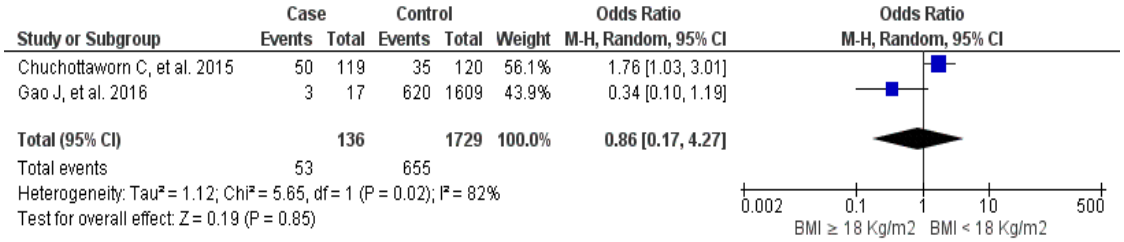
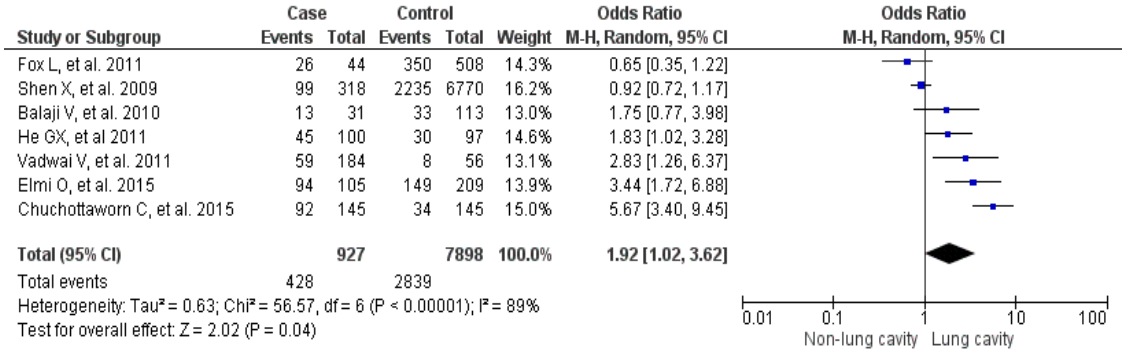


Figure E3. Heterogeneous effect estimated in several risk factors of MDR-TB stratified by area of study. *Notes*: TB: tuberculosis; reference group in each factor: (A) age less than 40 years, (B) HIV negative, (C) non-previous TB treatment; Citation of the studies refers to Table 1.

A. BMI (BMI≥ 18 Kg/m^2 vs. BMI < 18 Kg/m^2)



B. Lung Cavity (non-lung cavity vs. lung cavity)



C. Known contact with TB patient (no contact vs. contact)

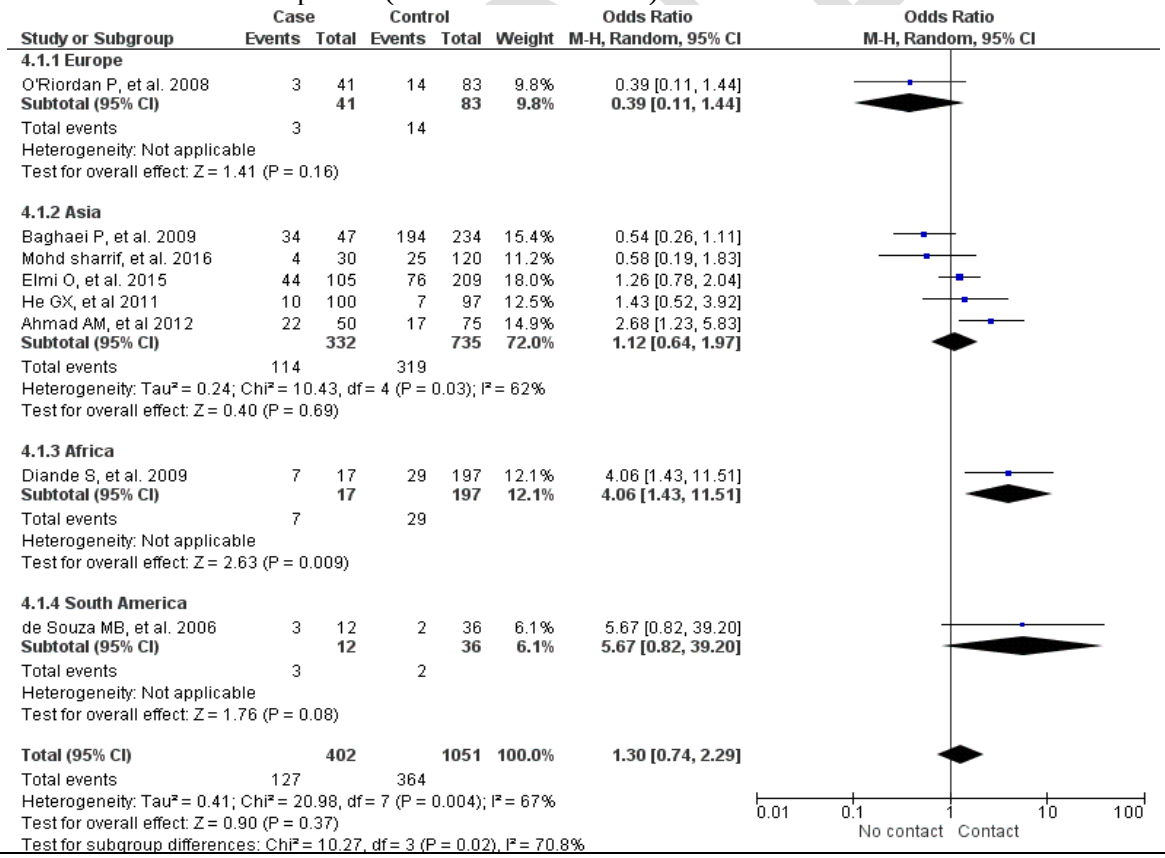


Figure E4. Heterogeneous effect estimated in several risk factors of MDR-TB. *Notes*: TB: tuberculosis; reference groups in each factor: (A) BMI ≥ 18 Kg/m^2, (B) non-lung cavity, (C) No contact with TB patient; BMI: body mass index; Citation of the studies refers to Table 1.